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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,662	04/09/2004	Jeff Blaney	20268-705.201	8787

21971 7590 03/26/2008
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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
03/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,662	BLANEY ET AL.	
	Examiner	Art Unit	
	JEFFREY LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,50 and 57-69* is/are pending in the application.

4a) Of the above claim(s) *5,58-60 and 64-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50, 57 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A Request for Continued Examination under 37 CFR § 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on January 9, 2008, has been entered.

Claims 5, 50 and 57-69, are pending in the instant application; claims 5, 58-60 and 64-69, are withdrawn as being directed to a non-elected invention; claims 50, 57 and 61-63, are the subject of the Office Action below.

Previous Rejections Withdrawn

Any previous rejections made in the Office Action mailed on October 9, 2007, and not reiterated in the instant Office Action below, are considered withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 50, 57 and 63, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nienaber *et al.*, *Nature Biotechnology 18*:1105-1108 **(2000)**, in view of Dauter *et al.*, *Acta Crystallographica D57*:239-249 **(2001)**, as evidenced by Wlodawer *et al.*, Nature Structural Biology 8(5):442-446.

Claim 50 is directed to a method for designing a lead candidate compound towards a biological target molecule comprising, combining the target with a mixture comprising two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties, followed by a structural determination, followed by the selection of "information" for the design of the lead candidate.

Nienaber teaches a method for screening a library of candidate compounds having binding affinity towards a given target biomolecule as a means towards developing a lead compound that has optimized binding properties. The method that Nienaber relies upon utilizes x-ray crystallography for making structural determinations, namely, by monitoring changes in the electron density of the biological target in the free and ligand-bound state (page 1105, col. 1, second paragraph). Nienaber exemplifies lead compound development using data from the binding of other ligands to the same target, and confirms it experimentally:

> "The primary screening data (structure) of compound 5 (Fig. 2A) bound to urokinase permitted a direct link to ***structure-directed lead optimization***. The structure reveals that the quinoline 8-position is directed toward a subsite termed the S1β pocket bounded by Gly 218, Ser 146, the Cys 191-Cys 220 disulfide bridge, the side chain of Lys 143, and part of Gln 19219 (Fig. 2B). In a previous study with the lead compound 2-naphthamidine, linking an amino-pyrimidyl group into this site was found to result in a substantial increase in binding potency (Ki = 5 μM to Ki = 0.03 μM, ref. 18, Fig. 2B), but the resultant compound exhibited no oral absorption. ***An overlay of the structures of the 8-aminopyrimidyl-2-naphthamidine and 8-hydroxy-2-aminoquinoline shows that although the directional vector from the 8-position of each molecule is different, the new lead can also access the S1β site (see Fig. 2B)***. To test this hypothesis, the ***8-aminopyrimidylsubstituted 2-aminoquinoline was synthesized*** and tested for inhibition as well as binding by crystallography. ***The optimized compound exhibited a 100-fold increase in inhibitory potency*** (Ki = 56 μM to Ki = 0.37 μM, Fig. 2C) that was similar to the boost conferred in the naphthamidine series."

Nienaber, page 1106, col. 2, last paragraph (emphasis added).

Although Nienaber utilizes x-ray crystallographic methods for determining the structure of the ligand bound to the biomolecule, Nienaber does not explicitly teach that the crystal having the biomolecule and ligand also comprises a second compound having anomalous dispersion properties, as in step 'a' of claim 50.

Dauter teaches a method for determining the crystal structure of pepstatin-insensitive carboxyl proteinase (PCP), by soaking a PCP crystal, wherein the PCP is bound with tyrostatin, in the presence of sodium bromide and lithium sulfate (see page 241, column 1). The sodium bromide has anomalous dispersion properties, which are used in the measurement, and are used to determine the structure of the PCP-ligand complex (see page 244, col. 2, paragraph 3, and reference to structure Wlodawer, which is cited in this rejection as evidence of the PCP-ligand structure). As in claim 63, Dauter teaches the use of bromine.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Nienaber, Dauter and Wlodawer, are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved x-ray technique and advances presented by Dauter, which are consistent for high-throughput screening, as in Nienaber for developing lead compounds based on the x-ray data obtained by screening a library of compound having binding affinity to a given biomolecule (see last sentence of Abstract in Dauter). Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Claims 50, 57 and 61-63, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nienaber *et al.*, *Nature Biotechnology 18*:1105-1108 **(2000)**, in view of Dauter *et al.*, *Acta Crystallographica D57*:239-249 **(2001)**, as evidenced by Wlodawer *et al.*, Nature Structural Biology 8(5):442-446, and in view of Reddy *et al.*, JACS 123:6246-6252 **(2001)**.

Claim 50 is directed to a method for designing a lead candidate compound towards a biological target molecule comprising, combining the target with a mixture comprising two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties, followed by a structural determination, followed by the selection of "information" for the design of the lead candidate.

Nienaber teaches a method for screening a library of candidate compounds having binding affinity towards a given target biomolecule as a means towards developing a lead compound that has optimized binding properties. The method that Nienaber relies upon utilizes x-ray crystallography for making structural determinations, namely, by monitoring changes in the electron density of the biological target in the free and ligand-bound state (page 1105, col. 1, second paragraph). Nienaber exemplifies lead compound development using data from the binding of other ligands to the same target, and confirms it experimentally:

> "The primary screening data (structure) of compound 5 (Fig. 2A) bound to urokinase permitted a direct link to ***structure-directed lead optimization***. The structure reveals that the quinoline 8-position is directed toward a subsite termed the S1β pocket bounded by Gly 218, Ser 146, the Cys 191-Cys 220 disulfide bridge, the side chain of Lys 143, and part of Gln 19219 (Fig. 2B). In a previous study with the lead compound 2-naphthamidine, linking an amino-pyrimidyl group into this site was found to result in a substantial increase in binding potency (Ki = 5 μM to Ki = 0.03 μM, ref. 18, Fig. 2B), but the resultant compound exhibited no oral absorption. ***An overlay of the structures of the 8-aminopyrimidyl-2-naphthamidine and 8-hydroxy-2-aminoquinoline shows that although the directional vector from the 8-position of each molecule is different, the new lead can also access the S1β site (see Fig. 2B)***. To test this hypothesis, the ***8-aminopyrimidylsubstituted 2-aminoquinoline was synthesized*** and tested for inhibition as well as binding by crystallography. ***The optimized compound exhibited a 100-fold increase in inhibitory potency*** (Ki = 56 μM to Ki = 0.37 μM, Fig. 2C) that was similar to the boost conferred in the naphthamidine series."

Nienaber, page 1106, col. 2, last paragraph (emphasis added).

Although Nienaber utilizes x-ray crystallographic methods for determining the structure of the ligand bound to the biomolecule, Nienaber does not explicitly teach that the crystal having the biomolecule and ligand also comprises a second compound having anomalous dispersion properties, as in step 'a' of claim 50.

Dauter teaches a method for determining the crystal structure of pepstatin-insensitive carboxyl proteinase (PCP), by soaking a PCP crystal, wherein the PCP is bound with tyrostatin, in the presence of sodium bromide and lithium sulfate (see page 241, column 1). The sodium bromide has anomalous dispersion properties, which are used in the measurement, and are used to determine the structure of the PCP-ligand complex (see page 244, col. 2, paragraph 3, and

reference to structure Wlodawer, which is cited in this rejection as evidence of the PCP-ligand structure). As in claim 63, Dauter teaches the use of bromine.

As in claims 61 and 62, Reddy teaches an iterative, computer-assisted, drug design strategy that combines molecular design, molecular mechanics, molecular dynamics (MD), and free energy perturbation (FEP) calculations with compound synthesis, biochemical testing of inhibitors, and crystallographic structure determination of protein-inhibitor complexes was successfully used to predict the rank order of a series of nucleoside monophosphate analogues as fructose 1,6-bisphosphatase (FBPase) inhibitors (see Figure 1, and description thereof; see Figure 3, and description thereof).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Nienaber, Dauter and Wlodawer, are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved x-ray technique and advances presented by Dauter, which are consistent for high-throughput screening, as in Nienaber for developing lead compounds based on the x-ray data obtained by screening a library of compound having binding affinity to a given biomolecule (see last sentence of Abstract in Dauter). Therefore the invention as whole was *prima facie* obvious at the time it was invented.

The further modification of the method of Nienaber and Dauter by Reddy would be a recognized advantage because of the accelerated pace and experimental confidence that established molecular dynamics simulations provide in lead compound development, especially considering that claim 50 reads on Nienaber and Reddy to the same extent. Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and

provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JSL/

/Jon D. Epperson/
Primary Examiner, AU 1639